can cause not only arthralgias but also chronic arthritis. It does not explain all cases, but one must all the same suspect it sometimes, and institute, in addition to the local treatment for the arthritis, a general treatment for the *B. coli* infection. Attention has also been drawn to the presence of *B. coli* by Dr. Beresford-Knox in a communication at the Liverpool Medical Institution; he stated that in numerous cases under his care *B. coli* was found in the urine, and that the condition of the joints improved with vaccine therapy. No details, however, were given in the report of any other physical signs or treatment.

Further investigation is undoubtedly necessary in this important issue, and may offer the lines for a new research. The role of the bowel in rheumatoid arthritis must be carefully reviewed, in view of the possibility that *B. coli* infection may have an intestinal origin. A careful bacteriological examination of the faeces was made in all our cases, but no abnormal flora were discovered. The following table gives a synopsis of the

Age	Catheter urine on admission	Faeces	Treatment	Arthritic symptoms. Result.
43	Alkaline. Trace of albumin—no casts, renal cells, or red cells. B.C.C. + on repeated examination	B.C.C. and enterococci only	Pot. cit. Aurotherapy	Marked improvement both in examination and from patient's point of view
50	Minute trace of albumin. No casts, vesical or blood cells. B.C.C. ++	No abnormal strains detected	Mandelic acid. Aurotherapy	Improved
55	Minute trace of albumin. Pus cells present, but no casts or renal cells. A few lower tract epithelial cells present. B.C.C. present	Nil abnormal	Citrates. Aurotherapy. Dental sepsis treated	Improved
48	Trace albumin, and a few leucocytes. B.C.C. present in cultures.	Nil abnormal	Pot. cit. Aurotherapy	Much improved
62	Trace albumin: a few leucocytes present. B.C.C. +	Nil abnormal	Pot. cit. Aurotherapy	Much improved
44	Trace albumin: few leucocytes and lower tract epithelial cells present. B.C.C. +	Nil abnormal	Pot. cit. Aurotherapy	Improved
53	Trace albumin: few leucocytes. B.C.C. + In 1925 exploration of a kidney was carried out for pyuria? and calculus, also cholecystectomy	Nil abnormal	Pot. cit. Aurotherapy	Improved
57	Trace albumin and lower tract epithelial cells present. B.C.C. +	Nil abnormal	Mandelic acid. Aurotherapy. Bladder washouts	No improvement
50	Vesical cells, and short-chained non-haemolytic streptococcus. Frequency of urine	Nil abnormal	Pot. cit. Enterophages by mouth	Improved

urine examinations, faeces examinations, and the treatment given. All the patients were females, and the arthritis in all cases was confirmed not only clinically but also by x-ray examination.

To sum up, we should like to draw attention to the association of: (1) *B. coli* with rheumatoid arthritis; (2) to the fact that bacteriological examination of the faeces in these cases proved them to be completely normal; (3) the arthritis and general condition of the patients having improved greatly with treatment of the *coli* infection; and (4) the existence of *coli* infection was completely unsuspected, there being urinary symptoms in only one of our cases.

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HISTIDINE TREATMENT OF PEPTIC ULCER

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It is well recognized that peptic ulcer constitutes an economic and social problem of some magnitude. The treatment of all the victims of this disorder as hospital in-patients is virtually impossible. It has been estimated that in some districts as many as one-third of the available medical beds would have to be in constant use for this one purpose if all the sufferers were to be accommodated. Almost every hospital has some scheme for the home treatment of such patients, but the success of any regime must depend upon the co-operation of the patient and of his doctor, and in no small measure upon the accommodation and financial resources of the patient's home.

Finally, in considering these cases, nothing less definite than the disappearance of a previously demonstrated radiological deformity can be accepted as evidence of healing, while no cure should be claimed in under seven years.

Diet and Alkalis

It has for many years been known that a large percentage of cases can be greatly improved by a careful dietetic regime combined with medicinal treatment. The various regimes are well known, and will not here be detailed; all involve complicated instructions, and are, without exception, irksome and difficult. Any new line of treatment in order to be generally acceptable must show results which are as good as those achieved by these well-established methods, and must also be more simple in use.

Parenteral Treatment

In view of the expense of in-patient treatment and the uncertainty of dietetics as practised in the average home, alternative methods of treatment have been sought. Many of these appear to have given good results, but the fact that none of them has become firmly established would suggest that they failed to satisfy the medical world of their superiority over the older methods.

Glaessner¹ has reported the use of injections of pepsin. This author assumed that excess of hydrochloric acid was the predominant factor in the genesis of peptic ulcers, and his treatment consisted in the injection of pepsin, rendered sterile by ultrafiltration, for two courses of thirty injections. It appears, however, that these cases while under treatment were also given careful dietetic instructions, and alkalis, olive oil, and belladonna, so the improvement can hardly be held to have been due to pepsin alone. Loeper, Debray, Michaux, and Sainton² used the same method, apparently quite independently, although the respective claims to priority gave rise to no little correspondence. Butman, Schultz, and Van Kleek³ draw an analogy between thrombo-angiitis obliterans and peptic ulcer, and suggest that the latter may result from an increased tendency to thrombosis. They treated a series of patients by intravenous injections of sodium citrate and sodium chloride carefully buffered to the correct hydrogen-ion concentration. Their results would appear to have been encouraging, but the radiological control rather inadequate.

Histidine Mono-hydrochloride

In the last two years attention has been increasingly focused upon the use of histidine mono-hydrochloride, and the preparation most extensively used has been larostidin.* The use of this substance is based upon a

* Marketed by the firm of Hoffmann-La Roche.

train of experimental work. In 1923 Mann and Williamson⁴ reported the results of their work in the experimental production of peptic ulcers in dogs. They pointed out that these animals are normally little susceptible to this disorder, and are therefore suitable subjects. Their methods all aimed at diverting the natural secretions of the duodenum which are supposed to neutralize the gastric acidity. They were able to perform duodenectomy and transplantation of the pancreatic and biliary ducts into the terminal ileum, but the most practicable technique was found to consist in duodeno-ileal anastomosis. This procedure fairly constantly resulted in the production of ulcers in the neighbourhood of the pylorus, and the ulcers so produced bore a very marked resemblance to peptic ulcers as found in human subjects. Weiss and Aron⁵ ten years later repeated this work in Strasbourg. They found that the absence of duodenal secretion prevented the digestion, and hence the assimilation, of albumins. The animals, after operation, suffered from cachexia, anaemia, atrophy of mucous membranes, and a peptic type of ulceration. They then proceeded to try in these animals the effect of the parenteral substitution of the various amino-acids, and the search was gradually narrowed down to tryptophan and histidine, and finally to histidine alone. It was shown that the injection of histidine would postpone indefinitely the appearance of ulcers, although it had little effect in counteracting the other results of the operation. They also found that exposure of these experimentally produced ulcers to a renewed flow of normal duodenal contents resulted in healing of the lesions.

This work is now well known, and upon it is based the use of histidine in the treatment of peptic ulcer as found in man. It will be seen that the scientific basis is rather frail and that very little analogy can be drawn between the experimental dogs with their mutilated gastro-intestinal tracts and human patients in whom no operation has been performed. There is, however, some similarity between the experimental ulcers and the marginal ulcers sometimes found after gastro-enterostomy. The results of the use of histidine in a series of these cases will be awaited with the greatest interest.

Immediate Results

Since histidine mono-hydrochloride first appeared on the market it has been used in many small series of cases, but they all of necessity have one common failing—they deal only with immediate results. There is general agreement that a varying percentage of cases show rapid and remarkable clinical improvement, while a rather smaller percentage furnish radiological evidence of the disappearance of the ulcer deformity. It is apparent that, until several years have elapsed, no useful purpose can be served by publication of further series of cases observed over only a short period of time unless the results in any particular series appear to differ greatly from those previously recorded. It would also appear that any conclusions drawn from the random application of this new therapeutic weapon can only serve further to confuse the issue. What would now seem to be needed is some means of determining which type of peptic ulcer is most likely to yield to treatment by histidine injections. I have already treated a considerable number of patients, but for the reasons given above do not intend to make any reference to this series as a whole, although the early results in the case of ulcers of the lesser curvature seem to be less favourable than those previously reported.

Role of Histidine

Histidine is one of the essential amino-acids produced as a result of protein digestion, and is thought to be necessary for cell life. This statement is, of course, so absurdly vague as to be almost meaningless, and it

remains true that the mode of action of histidine in promoting the healing of peptic ulcers is still entirely a matter for speculation. J. T. Eads⁶ suggests that it may be either a factor necessary to cell integrity and repair, or that it may be effective by causing a secretion rich in the protective and acid-combining mucin. In this connexion the work of C. R. Jones,⁷ who tried the effect of the oral administration of mucin as an adjuvant to other methods of treatment, is of some interest. The results seem to have shown an improvement over those obtained by ordinary medical methods, but there is no record of this technique having been tried by any other workers.

The usual therapeutic procedure is to give a course of twenty-one injections either subcutaneously or intramuscularly. The injections are given on consecutive days, and each consists of 5 c.cm. of a 4 per cent. solution of histidine mono-hydrochloride. In no case has any undesirable reaction been reported. Some workers have, in addition, given histidine in tablet form by mouth.

Survey of Published Cases

Many series of cases have now been published in this country and abroad. David Smith⁸ reports twelve cases of ulcer of the lesser curvature in all of which clinical and radiological evidence of healing was forthcoming. Bulmer,⁹ in a much-quoted paper, reports fifty-four cases, with the following immediate results: thirty cases, comprising eight of duodenal and twenty-two of gastric ulcer, became symptom-free and exhibited a normal radiograph after treatment; ten cases, comprising three of duodenal and seven of gastric ulcer, became symptom-free, but in this group the radiograph remained abnormal. In the third group there are found twelve patients in whom the treatment frankly failed. In this last group duodenal and gastric ulcers are equally represented. This is one of the largest series so far reported, and it will be seen that the results are distinctly encouraging.

Hessel¹⁰ reports twenty-two cases, in eighteen of which the ulcer was situated in the duodenum. In sixteen cases the ulcer could no longer be demonstrated radiologically after treatment, while in the remaining six marked diminution in size was recorded in every case. Most of the patients showed a substantial gain in weight, while several, who had previously shown a gastric hyperacidity, gave curves which after treatment approached more nearly to normal.

Bogendoerfer¹¹ reports results in the treatment of thirty cases. No detailed analysis is given, but all the patients are claimed to have shown improvement. Volini and McLaughlin¹² had satisfactory results, and report on both clinical improvement and reduction in gastric acidity.

Eads⁶ has recorded a series of thirty-five cases, thirty of which were duodenal and only five gastric ulcers. The immediate results show that six cases gave clinical and radiological evidence of healing, eight cases gave clinical and radiological evidence of improvement, nine cases gave evidence of amelioration of symptoms but showed no radiological change, while twelve cases were unimproved at the completion of a course of treatment.

Raffsky,¹³ in a study of twenty-four cases, one only of which was a gastric ulcer and one a marginal ulcer, found in eighteen symptomatic relief.

Discussion

From this brief survey of the published cases it will be seen that the preliminary results have been very encouraging. It is claimed that histidine may be successfully given to ambulant patients who remain at work throughout, and that no other treatment is necessary. Nevertheless, many of the patients included in the series analysed above were actually at rest in bed during the

greater part of their treatment. Now it is known that peptic ulcers are capable of undergoing spontaneous remission, and that rest in bed is a valuable part of the routine medical treatment. It is therefore possible that in some of the series the good results may be attributable, in part at least, to rest and regular meals, with prohibition of alcohol and limitation of smoking. Further, the psychological aspect of peptic ulceration has lately been emphasized, and it may be that the mere institution of hospital in-patient treatment may in itself produce a beneficial effect, just as patients suffering from carcinoma of the stomach are known to make a striking temporary improvement after admission to hospital and again after laparotomy.

Secondly, it is perhaps confusing that the American and Continental series contain so high a proportion of duodenal ulcers, for the radiological demonstration of ulcers in this situation is notoriously much more difficult than in the case of those in the stomach.

It is to be hoped that future published work on this subject will deal only with ulcers which have been demonstrated radiologically and whose disappearance has been verified by the same means, and also that any cases in which ancillary treatment has been permitted will be rigidly excluded.

It is obvious that some cases of peptic ulceration respond well to histidine therapy. What is now required is a means by which these cases may be identified.

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Clinical Memoranda

Histidine Treatment of Peptic Ulcer

The results which have been obtained with histidine in general practice are quite as remarkable as those recorded by Mr. R. J. McNeill Love in the *Journal* of March 21st (p. 582). Of fourteen cases of peptic ulcer that received histidine treatment only two failed to react favourably. Marked success was obtained in a case where bleeding was taking place, and this case is worth recording fully.

CASE REPORT

A male patient, aged 44, presented himself at the surgery with a history of haematemesis of two days' duration. The man had been a shop-assistant up to four years ago, when he became unemployed; for the last ten months he had been working as a labourer at a foundry. It was then that he began to be troubled with "indigestion and wind" and pains in the pit of the stomach, which came on about half an hour after food. This he attributed to the fumes, the smoke, and the heavy nature of his work. Although he had often felt sick, he vomited for the first time two days before, when he brought up about a cupful of dark brown material. He vomited six times altogether, and there was present each time in the vomit the same dark brown material. He was advised to go to bed immediately, but he refused to do this, as he would have lost his job. It was with difficulty that he was persuaded to stay away the few days necessary for an x-ray film to be taken. The radiologists reported the presence of a large-sized ulcer of the middle of the lesser

curvature of the stomach. The patient was started on a course of histidine injections, and given an alkali powder to carry with him, to be taken three-hourly. Each Saturday afternoon he went to bed and remained there until Monday morning. The brand of histidine used was "stellidin,"* and at the end of a fortnight the patient volunteered the information that a whole day had passed and he had experienced no pains. In all he received thirty-five consecutive injections, and another x-ray film was then taken, the radiologist reporting: "The ulcer, which was easily displayed a month ago, could not now be shown at all; nor was there any tenderness at the ulcer site. This must mean that the ulcer is nearly, or quite, healed. The only abnormal feature was a small residue at six hours." Since then the man has been quite free of all symptoms except "wind" after heavy meat meals.

In each of the fourteen cases of ulcer treated only radiological evidence was accepted as to the original presence and the subsequent healing of the ulcer. Results were as follows:

Eleven Cases.—Symptoms disappeared and ulcer healed radiologically.

One Case.—Symptoms definitely relieved, but ulcer still present.

Two Cases.—No relief from symptoms and ulcer still present.

In the last two cases one of the patients is an inveterate spirit drinker, while the other man, a patient suffering from duodenal ulcer, was relieved of all symptoms for about two weeks after a course of injections, but he was then involved in a motor accident, where the severe impact of the driving wheel against his abdomen caused the reappearance of the train of symptoms, which are now no longer amenable to any form of medical treatment.

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Spontaneous Haematoma of Abdominal Wall

The report of Mr. Robert Mailer's case of spontaneous haematoma of the abdominal wall (March 28th, p. 637) is of interest to us in view of a similar case which came into the Royal South Hants Hospital a few weeks ago.

A married woman, aged 68, was admitted to hospital on February 26th. She had been in good general health, but for seven days previously had suffered from dull aching pain in the left lower abdomen, which had not prevented her from continuing with her usual work. Seven hours before admission she had been seized with sudden acute pain at the same site in the left iliac fossa, and had since vomited three times. There was a history of mild chronic cough, but not of any previous attacks of pain at this site.

On examination the patient was pale and shocked, and obviously suffering from a good deal of pain. The abdomen was resistant to examination, and there was a tense, tender swelling to the left of the mid-line, which on palpation appeared to extend up to the umbilical level on the left, down across to the right side of the pelvis. On pelvic examination it was difficult to outline the swelling on account of the resistance to, and tenderness on, bimanual examination. Temperature was 97.2° F., pulse 80, and there were no abnormal constituents in the urine.

A diagnosis of twisted ovarian cyst was made, and the patient prepared for immediate operation. A left paramedian incision was made, and on opening the rectus sheath a large haematoma was exposed. About ten ounces of clot was removed, but no bleeding point could be found. Even after this was removed there was still an obvious abdominal mass present. The peritoneal cavity was opened and a right broad ligament cyst was found. It was about nine inches in diameter, and although fairly tense showed no sign of any complication. It was dissected out and removed. The torn rectus muscle was too macerated to suture, and a small

* The preparation—"stellidin"—is manufactured by May and Baker, and it was found to cause less pain at the site of injection than the other histidine preparations.